

Differential Antibiotic Excretion in Unilateral Structural Pyelonephritis

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Differential antibiotic excretion studies in eight patients with unilateral structural pyelonephritis showed that in all instances there was impairment in antibiotic excretion on the affected side compared with the normal kidney. Both peak and mean urinary concentrations were decreased on the structurally abnormal side. The degree of defect in antibiotic concentration was proportional to the amount of unilateral medullary damage, as measured by differential renal function studies. While the antibiotic concentrations achieved had an inconsistent relationship to cure in three patients with proven unilateral infections, the striking decreases in urinary antibiotic levels may argue against oral penicillin-G treatment of unilateral pyelonephritis in which there is renal parenchymal damage.

THE EFFECTIVENESS of penicillin-G against most Gram-negative organisms *in vitro* is well recognized and its use in treating urinary tract infection has been advocated. This treatment is usually recommended for infra-nephric infections, however, and great reliance is placed on the increased urinary concentration of antibiotic to promote its effectiveness.¹⁻³ Oral penicillin-G at a dose of 3.2 million units per day when administered without food has been shown to produce mean urinary concentrations of antibiotic in excess of 300 μ g per ml in normal volunteers.⁴ These data have recently been substantiated by Hulbert.⁵ Such con-

centrations exceed the minimum inhibitory concentration (MIC) for most urinary pathogens. Stamey⁶ has advocated therapy with penicillin-G for susceptible organisms, and good results in the treatment of bacteriuria emanating from the upper tract are documented by ureteric catheterization.

In the presence of infected urinary calculus disease, in urologic obstruction with infection or in renal failure, therapeutic urinary levels either may not be achieved or, if achieved, may be ineffective in clearing the infection. In these instances intensive antibiotic therapy is crucial, usually with associated surgical treatment except in chronic renal disease. Similar frustration of therapy occurs in *unilateral* structural pyelonephritis where severe parenchymal damage has occurred. We have noted in such cases that despite appropriate treat-

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ment based on sensitivity testing, it is the exceptional patient who is cured of infection with urinary level antibiotic therapy. Failures in such patients could be attributed to micro-abscesses interfering with antibiotic perfusion of medullary tissue within the renal parenchyma, or to the presence of micro-calculi serving as reservoirs of infection. Either explanation is possible since the identical organism recurs after appropriate therapy in most instances, usually with unchanged antibiotic sensitivities. A third possibility is the failure of impaired tubular concentrating mechanisms on the involved side to achieve sufficient medullary antibiotic levels to clear the infection. In order to test this third hypothesis, eight patients with unilateral structural pyelonephritis were studied by ureteric catheterization. Standard renal function tests were made and differential antibiotic concentrations were determined.

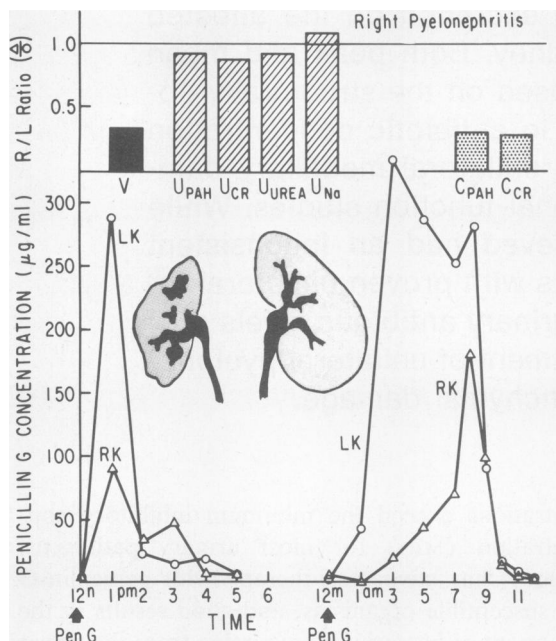


Chart 1.—Documented Right Pyelonephritis. Urine volume, U_{PAH} , U_{CR} and U_{Lrea} are all decreased with an increase in U_{Na} on the infected side compared with the normal kidney. Clearance ratios show marked functional impairment on the right side. Peak urinary penicillin concentrations are substantially greater in the non-infected left kidney. Mean urinary penicillin concentration on the right was 31 μg per ml and was 57 μg per ml on the left (Table 1).

The *P. mirabilis* isolated from the right kidney was found to be resistant to penicillin-G (MIC = $>512 \mu\text{g}$ per ml). Here the MIC far exceeded the concentration of 31 μg per ml in the right renal urine. The patient remains asymptomatic when given maintenance dosages of ampicillin although *P. mirabilis* can be recovered from urine when therapy is interrupted.

Methods

In eight women patients with a history of recurrent urinary tract infections, the results of excretory urography were consistent with unilateral atrophic pyelonephritis. In all affected kidneys a decrease in renal size was apparent and there was cortical scarring adjacent to blunted calyces. The contralateral kidney showed no consistent calyceal changes and in most instances was enlarged. Additional urologic work-up showed vesicoureteral reflux in two patients. One patient was being evaluated for hypertension and inactive unilateral renal tuberculosis. In five of the eight patients

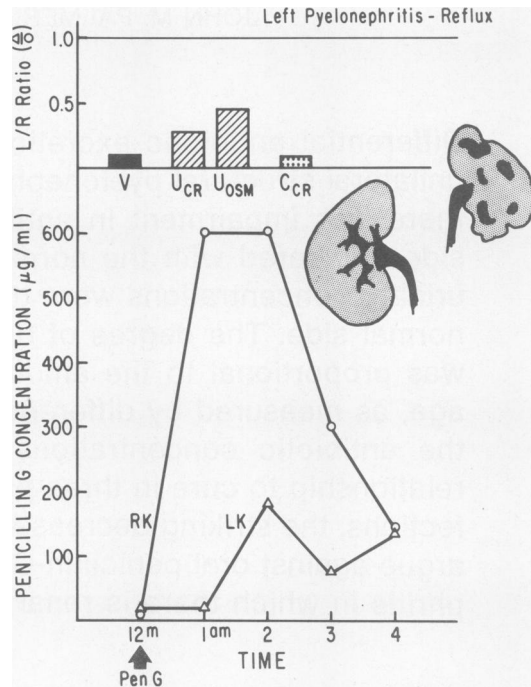


Chart 2.—Documented Left Pyelonephritis. Urine volume, U_{CR} and U_{OSM} (osmolality) ratios are severely reduced in this patient with proven left renal infection. The damaged left kidney constitutes less than 10 percent of the total renal function. Urinary penicillin concentration peaks at 600 μg per ml on the normal side, over three times the level achieved on the infected side. The comparative delay in peak concentration probably relates to dead-space error from low urine volume on left. The mean left urinary concentration was 87 μg per ml, less than 30 percent achieved on the right side (Table 1).

Left vesicoureteral reflux was present. The *E. coli* recovered from the left kidney was sensitive to penicillin-G at 38 μg per ml. Mean urinary concentrations from this kidney exceeded this at 87 μg per ml. Despite this, repeated courses of penicillin-G failed to clear this *E. coli* which recurred within several days of cessation of therapy. Although serotyping was not done, repeat testing showed identical sensitivity. Long term therapy with cephaloglycin was equally ineffective and nephrectomy was ultimately necessary to control morbidity from infection.

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differential ureteric catheterization studies localized the infection unilaterally to the abnormal kidney. In no instance was infection found on the contralateral side. Two patients were not infected at the time of antibiotic excretion studies and one had infection confined to the bladder.

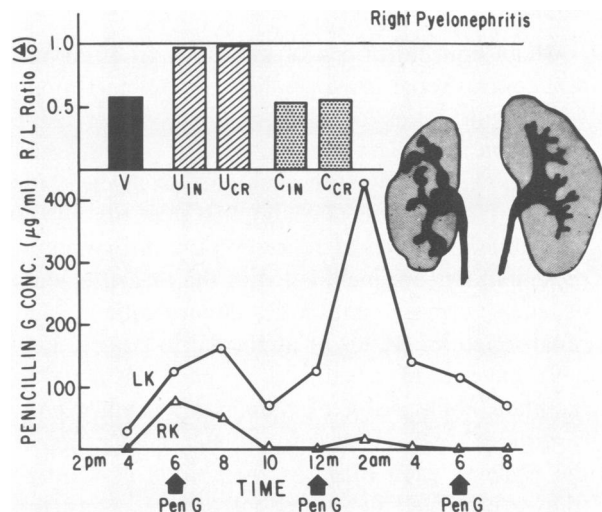


Chart 3.—Documented Right Pyelonephritis. Minimal differences in U_{IN} and U_{CR} are present in this patient during hydration, despite depressed clearance values on the infected right side. During the antibiotic excretion study consistently lower concentrations were found on the right side, although the mean concentration ratio of 0.11 (Table 1) is probably skewed by the peak concentration of 400 μ g per ml on the normal side after the second dose.

The *E. coli* isolated from the right kidney was sensitive to penicillin-G at 49 μ g per ml. The mean concentration of antibiotic in the urine was only 16 μ g per ml during the study, but the two peak concentrations exceeded the MIC for the organism. Treatment with penicillin-G cleared this infection, although subsequent infections with different organisms have required intermittent therapy.

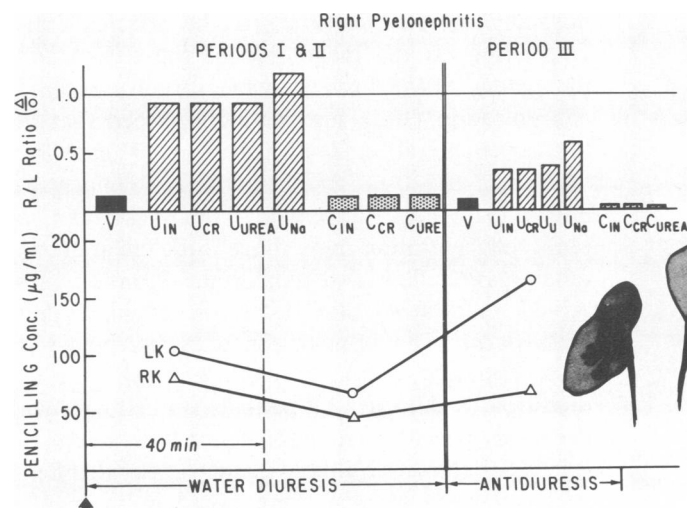


Chart 4.—Documented Right Pyelonephritis. During the first two 40-minute collection periods minimal differences in U_{IN}, U_{CR} and U_{UREA} are shown on the right side along with some impairment in tubular reabsorption of sodium. Penicillin concentration ratios approach those of inulin during these periods but digress during period three when, following emesis, she became antidiuretic and the greater concentrating ability of the left kidney became apparent. Mean concentration of penicillin on the right side was 65 μ g per ml (Table 1). This patient was lost to follow-up.

After collection of the final ureteric specimen for urine culture, appropriate oral antibiotic therapy was begun. Six patients were treated with penicillin-G, one with cephaloglycin, and one with nalidixic acid. In each patient, a ureteral catheter of ample size to collect all urine flow was left in place on the affected side and fixed to an indwelling bladder catheter which delivered the urine from the normal kidney. These catheters remained in place for subsequent urine collections for antibiotic excretion studies and renal function tests.

Antibiotic Excretion Studies

Urine specimens were quick-frozen until thawed for antibiotic assay. Urinary antibiotic concentration was determined by large agar plate bioassay using *Bacillus subtilis*. Urine specimens were diluted to 1:200 with sterile 0.1 normal saline solution and 0.02 ml was placed in prepared wells within the seeded nutrient agar plate. Antibiotic standards ranged from 100 μ g per ml down to 6.5 μ g per ml. Using a volumetric pipette 0.02 ml of several of these dilutions were inserted into wells on the same agar plate. The solution wells were arranged in four parallel rows, containing counter-linear antibiotic concentrations and diluted urine. The plates were incubated at 37°C (99°F) for 24 hours. Zone size indicating antibiotic activity was measured with a vernier caliper and plotted on semi-log paper against the logarithm of the concentration. This gave a mid-point linear curve between 1 and 100 μ g per ml relating the magnitude of the inhibitory zone to the concentration of antibiotic.^{4,7}

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TABLE 1.—Data on Concentration of Antibiotic in Abnormal and Control Kidney

Patient and Chart	Antibiotic Used	Mean Urinary Concentration ($\mu\text{g per ml}$)		Ratio I/N*
		Abnormal Kidney	Control Kidney	
1 ..	Penicillin-G	31	57	0.55
2 ..	Penicillin-G	87	331	0.26
3 ..	Penicillin-G	16	140	0.11
4 ..	Penicillin-G	65	111	0.58
5 ..	Penicillin-G	180	315	0.57
6 ..	Penicillin-G	67	80	0.84
7 ..	Cephaloglycin	706	1,100	0.64
8 ..	Nalidixic Acid	41	123	0.33

*Ratio of infected to normal kidney.

Renal Function Studies

At least three consecutive one-hour urine collection periods were averaged in each patient to arrive at accurate values for differential urinary creatinine concentrations (U_{Cr}) or inulin concentrations (U_{In}). In two patients P-aminohippurate (PAH) was infused at a constant rate to evaluate urinary PAH concentration (U_{PAH}) and clearance (C_{PAH}). Clearances of In, PAH and Cr were calculated where applicable. Urine volumes, concentrations and clearances in each patient were then expressed as a ratio of the measurements on the

affected (abnormal) side to those of the opposite (normal) kidney. Studies were performed under varying degrees of hydropenia. No attempt was made to measure maximal urine concentrating ability, but three patients were studied while anti-diuretic.

Results

Mean concentrations of antibiotic in abnormal and control renal urine are listed in Table 1 along with mean ratios of abnormal to control urine concentrations. The specific results of individual patient experiments are included as legends for Charts 1 through 8. To simplify presentation of data, line-drawings of representative urograms in these patients are included with the measurements of their urinary antibiotic concentrations and renal function. Ratios of abnormal to control kidneys have been calculated in each instance to facilitate comparison of data, with urinary concentration ratios at the left and clearance ratios at the right of each diagram. Antibiotic concentrations are plotted in $\mu\text{g per ml}$ and represent the mean concentration achieved in urine from each kidney during the period of collection (usually hourly periods). All patients received antibiotic (800,000 units of penicillin-G before meals, or 250 mg of cephaloglycin or nalidixic acid by mouth) at time indicated by arrows on the abscissa.

Discussion

The renal pathophysiology of unilateral pyelonephritis has been well documented.⁸ The medullary defect results in impaired tubular reabsorption of filtered sodium (and obligate water) leading to a decrease in concentration of substances normally excreted in urine on the affected side. Depending on the magnitude of the defect and the extent of nephron damage, urinary sodium concentration (U_{Na}) may actually exceed that in the contralateral kidney (Charts 1, 4 and 5), while U_{Cr} , U_{In} , U_{PAH} and urinary urea concentrations (U_{Urea}) are decreased. These disorders in renal concentration may have little relation to renal plasma flow and glomerular filtration rate (GFR) until substantial losses in nephron unit mass occur. The tubular concentrating defect is most apparent during dehydration, and can be obscured by diuresis. All patients studied had evidence for unilateral functional impairment but in varying degrees. Minimal concentrating differences between kidneys were noted in three pa-

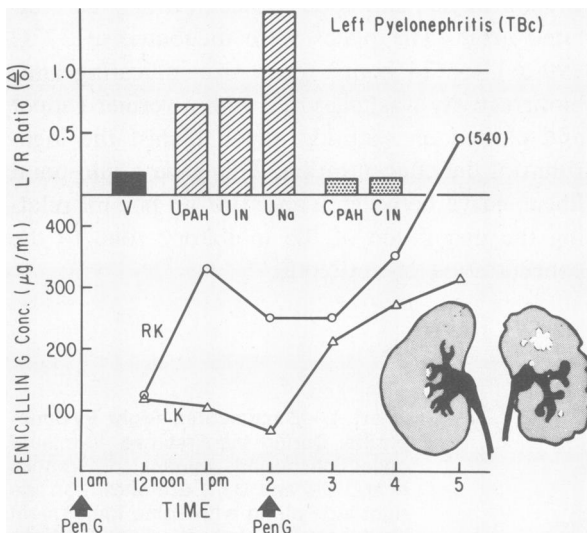


Chart 5.—Patient Uninfected at Time of Study. Urine volumes were significantly reduced from the damaged left kidney with a dramatic defect in tubular reabsorption of filtered sodium compared to the opposite side. Clearances of PAH and In are impaired on the left. Penicillin urinary levels on the left were considerably below those achieved on the right as evidenced by Chart 5 and Table 1.

This patient had been treated for tuberculosis of the urinary tract and was being evaluated for hypertension. Routine and acid-fast cultures were sterile at the time of study.

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tients (Charts 1, 3 and 4), while more obvious changes were shown in the remaining patients. These variations are probably not significant since all function studies were done under water diuresis. All patients tested had pronounced renal functional impairment on the involved side as measured by comparative clearance studies.

In seven patients substantial differences between the two kidneys were noted in urinary antibiotic concentrations. These concentration differences were often more extreme than differences in U_{Cr} but they represent a truer estimate of maximal tubular function since water diuresis (initiated during the bacteriologic localization study) had been overcome. Maximal urinary concentration of antibiotic on the involved side was never greater than half that achieved in urine from the normal kidney and was one-third or less of the peak normal concentration obtained in six patients. In three of six patients studied during administration of oral penicillin-G, the abnormal kidney failed to achieve the minimal therapeutic concentration of 100 μg per ml (Charts 3, 4 and 6). In two of the remaining patients, peak concentrations were

less than 200 μg per ml (Charts 1 and 2). Mean concentrations of antibiotic are perhaps more meaningful since they more closely represent effective therapeutic delivery. Mean urinary concentrations of penicillin-G were less than 100 μg per ml on the abnormal side in five of six patients studied (Table 1).

Maximal urinary concentrating ability was found by Ronald and coworkers⁹ to be impaired in patients with proven upper urinary tract infections. They also noted an improvement in overall concentrating ability approaching 100 milliosmols (mosm) per Kg in the majority of those studied after eradication of bacteriuria. That the concentrating defect was reversible may have some application to antibiotic excretion data in the present study. Certainly, impaired urinary antibiotic excretion in active pyelonephritis may be related to acute tubular damage. In four of these patients, however, no active renal infection was documented and yet all had decreased antibiotic excretion on the involved side, consistent with renal tubular disease.

Renal clearance of penicillin-G has been esti-

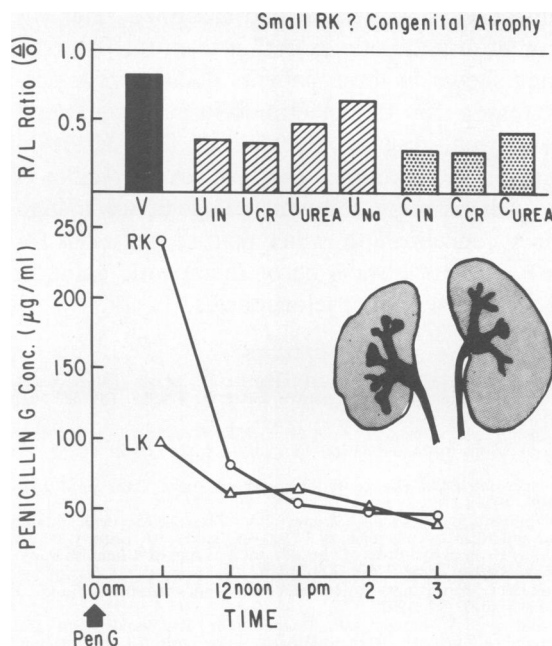


Chart 6.—Patient Uninfected at Time of Study. A substantial impairment in renal tubular function is present on the right side, evidenced by low right to left ratios for the various parameters. Renal clearances are similarly decreased. Penicillin-G concentration in urine from the damaged right kidney fails to approach the peak concentration achieved on the left side after oral administration. Mean concentrations of antibiotic were 67 μg per ml on right and 80 μg per ml on left (Table 1).

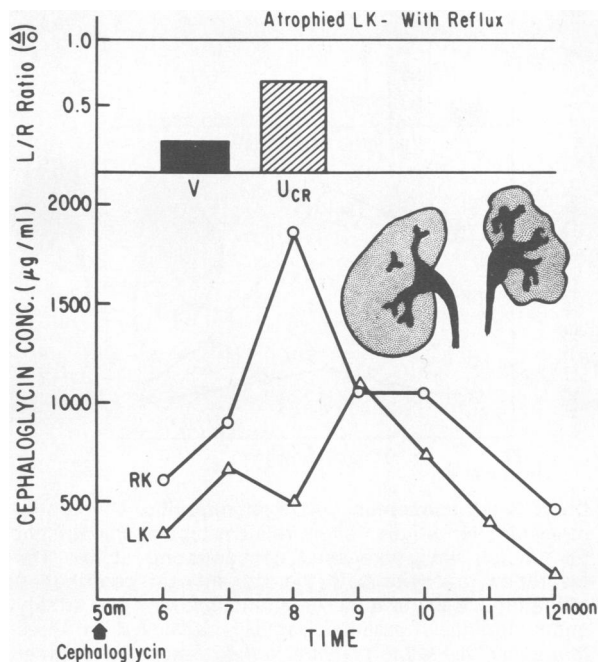


Chart 7.—Infection Localized to Bladder. Urine volume was low with a decrease in U_{Cr} from the structurally abnormal left kidney in this unilaterally refluxing patient. Peak antibiotic concentration was higher and occurred earlier in tests of the urine from the right kidney. Mean concentration on the left was less than two-thirds of that on the right (Table 1).

mated in excess of 380 ml per minute per 1.73 square meters of body surface area.¹⁰ Since this figure exceeds that for GFR, tubular excretion plays a prominent role in delivery of this antibiotic to the urine. It follows that medullary damage from recurrent pyelonephritis will impair urinary antibiotic concentration not only by presenting a more dilute urine to the collecting duct, but by interfering with the usual tubular mechanism of penicillin excretion. In these patients, all with unilateral structural pyelonephritis, substantial defects in penicillin, sodium cephaloglycin and nalidixic acid excretion on the involved side have been shown. Excretion of antibiotic in the urine from the abnormal kidney ranged from 84 percent down to only 11 percent of the urine concentrations achieved in the control kidney. Charts 1 through 8 also suggest a relatively fixed antibiotic excretion capacity on the abnormal side along with the low concentrations. Although it is not specifically proven by these data, one might suspect that administration of larger doses of antibiotic would only result in increased urine levels from the control kidney.

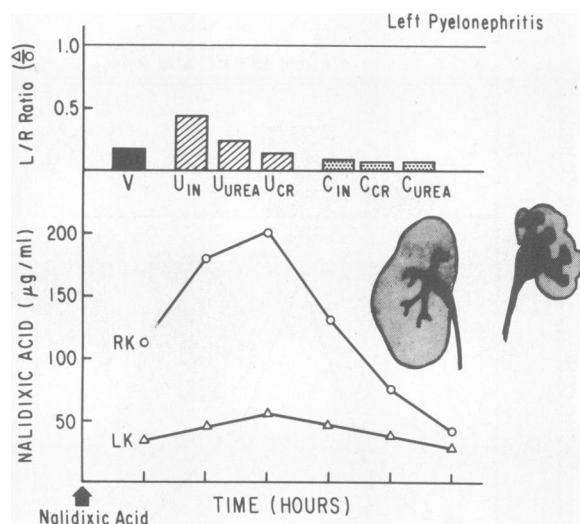


Chart 8.—Documented Left Pyelonephritis. Differential renal function studies show relative tubular impairment on the left with decreased concentrating ability. The clearance ratios indicate the insignificant contribution of the left kidney to total renal function. Maximal urinary concentration of nalidixic acid is achieved in three hours, but the abnormal left kidney reaches only one-fourth the magnitude of that on the right side. Mean antibiotic concentration on the left was 41 µg per ml (Table 1).

P. mirabilis was isolated from the renal urine. Because of penicillin allergy, nalidixic acid was selected (MIC = 25 µg per ml). The mean antibiotic concentration of 49 µg per ml exceeded the MIC and therapy was successful although subsequent repeated infections with different organisms have resulted in nephrectomy.

In the three infected patients where these data are significant (patients 2, 3 and 8), there was an indeterminant relationship of the urinary levels achieved to cure. In patient 2, pyelonephritis persisted with the same generic organism maintaining a similar sensitivity pattern despite urinary antibiotic concentrations in excess of the MIC. In patient 8, the urinary levels of penicillin exceeded the relatively low MIC for the organism (*P. mirabilis*) and treatment was initially effective. In patient 3, however, the infection was cured despite mean urinary antibiotic concentrations from the involved kidney well below the MIC for the organism (two peak concentrations exceeded this figure, however). Clearly, it is necessary to evaluate a larger number of patients before the relationship of impaired antibiotic excretion in unilateral pyelonephritis to the cure of parenchymal infection can be fully appreciated.

Finally, two patients required nephrectomy for ultimate control of morbidity from infection. While some observers would consider such an ablative procedure extreme in pyelonephritis, in well documented cases of recurrent unilateral infection where the involved side contributes only marginally to total renal function, surgical cure of infection is impressive and sustained. The impairment in antibiotic excretion from the involved kidney shown in these patients documents a possible cause for therapeutic failure in unilateral parenchymal disease. Because of this defect in urinary concentration, the use of penicillin-G (and other antibiotics which depend upon high urinary concentration rather than serum levels for cure) may not always be of therapeutic value in unilateral structural pyelonephritis.

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